REMARKS

Claims 1, 2, 5-8 and 11-16 are pending in the subject application. Applicants hereinabove have amended claims 1, 6, 7, 11, and 14, and cancelled claims 2, 5, 12, 13, 15, and 16 without disclaimer or prejudice to applicants' right to pursue such claims in the future. Accordingly, upon entry of this Amendment, claims 1, 6-8, 11, and 14 will be pending and under examination.

Applicants maintain that the amendments to the claims 1, 6, 7, 11, and 14, do not raise any issue of new matter, and these claims, as amended, are fully supported by the specification as originally filed.

Support for the claim amendments is found, *inter alia*, in the specification as follows: **Claim 1**: page 4, line 21 to page 5, line 8, page 10, lines 4-8 and 10-16, page 21, line 15 to page 22, line 21, page 23, lines 6-8, page 24, line 24 to page 25, line 17, page 28 (Table 4), page 40, lines 27-32, and page 46, line 28 to page 47, line 4; **Claim 6**: page 9, lines 22 and 23, and page 40, lines 35-36; **Claim 7:** page 4, line 21 to page 5, line 8, and page 40, line 35 to page 41, line 2; and **Claims 11 and 14:** page 4, line 21 to page 5, line 8, page 10, lines 4-8 and 10-16, page 21, line 15 to page 22, line 21, page 23, lines 6-8, page 24, line 24 to page 25, line 17, page 28 (Table 4), page 40, lines 27-32, and page 46, line 28 to page 47, line 4.

In view of the comments set forth below, applicants maintain that the grounds of the Examiner's rejections

made in the August 11, 2004 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw these grounds of rejection.

Formalities

The Examiner stated that the request for a continued prosecution application (CPA) under 37 C.F.R. §1.53(d) filed on April 21, 2003 is acknowledged. The Examiner stated that 37 C.F.R. §1.53(d) was amended to provide that the CPA must be for a design patent and the prior application of the CPA must by a design application that is complete as defined by 37 C.F.R. §1.51(b). Citing Elimination of Continued Prosecution Application Practice as to Utility and Plant Patent Applications, final rule, 68 Fed. Reg. 32376 (May 30, 2003), 1271 Off. Gaz. Pat. Office 143 (June 24, 2003). The Examiner also stated that since a CPA of this application is not permitted under 37 C.F.R. §1.53(d)(1), the improper request for a CPA is being treated as a request for continued examination of this application under 37 C.F.R. §1.114.

Rejections Under 35 U.S.C. §103(a) - Obviousness

The Examiner rejected claims 1, 2, 5-8, 11, 14 and 15 under 35 U.S.C. §103(a) as allegedly unpatentable over Jennemann et al. in view of Vangsted et al. and Kensil et al.

The Examiner stated that applicants argued that the combination of the cited references do not teach or suggest the combination of a composition comprising a

fucosyl GM1 ganglioside-KLH conjugate with a QS21 carbohydrate as instantly claimed. The Examiner also stated that it is noted that the Examiner was in error by stating that the Jennemann et al. taught the composition comprising fucosyl GM1-KLH conjugate with a QS21 carbohydrate. However, the Examiner stated that Jennemann et al. provides sufficient motivation for those of skill in the art to use the fucosyl GM1-KLH conjugate with QS21, because the article relied upon by Jennemann et al. (i.e., Livingston et al., Vaccine, 12(14):1275-1280, IDS January 29, 2002, exhibit 13) taught the effectiveness of a composition comprising a GM2 ganglioside conjugated to KLH with a QS21 adjuvant and further indicated the ability to such an adjuvant to be effective in treating malignant melanomas. The Examiner also stated that because it was well known in the art at the time the invention was made that adjuvants such as QS21 were effective in generating high adjuvanicity and carried a low amount of toxicity, one of skill in the art would readily substitute one for the other based on these characteristics (citing page 1276 of Livingston et al.). The Examiner also stated as noted by the applicants on page 7 of the response filed April 21, 2003, Kensil et al. indicates that QS21 has the ability to boost the responses of adjuvants such as KLH. The Examiner concluded that given the suggestion of Jennemann et al. in combination with Vangsted et al. and Kensil et al. one of ordinary skill in the art was provided ample motivation to use QS21 in place of MPL based on adjuvancity, low toxicity and its ability to boost the effects of KLH and thus a composition comprising a fucosyl GM1-KLH and QS21 would be reasonably expected to

elicit an enhanced ability to induce an immune response.

The Examiner also stated that the applicants also argues that the Examiner misinterprets the term "similar" when applied to the carbohydrates, stating that there is no indication of "similarity" between Fuc-GM1 and Glac2 ganglioside. The Examiner stated that the applicants' arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. The Examiner stated that irregardless of applicants' statements, the motivation using QS21 in place of MPL was provided by Jennemann et al. The Examiner also stated that all other arguments concerning "similar" language is irrelevant because these are arguments of counsel of which are unsubstantiated. The Examiner stated that the term "similar" as used by Jennemann et al. could be applied in either light and applicants have not provided sufficient objective evidence that would refute that Fuc-GM1 is not similar to Glac2. To some degree, Fuc-GM1 is "similar" to Glac2 in that both are gangliosides.

In response to the Examiner's rejection to claims 2, 5, and 15, applicants note that these claims have been cancelled. Thus, the Examiner's rejection of claims 2, 5, and 15 is now moot, and request that the Examiner reconsider and withdraw this ground of rejection.

In response to Examiner's rejection to claims 1, 6-8, 11, and 14, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Briefly, claim 1, as amended, provides a composition which comprises (A) a conjugate of i) a derivative of a fucosyl GM1 ganglioside which comprises a converted ceramide portion, which differs from the ceramide portion of the fucosyl GM1 ganglioside solely by having an aldehyde group in place of a double bond, and ii) Keyhole Limpet Hemocyanin, wherein the derivative of fucosyl GM1 ganglioside is covalently conjugated to Keyhole Limpet Hemocyanin by a covalent bond between an amino group of Keyhole Limpet Hemocyanin and the aldehyde group of the converted ceramide portion of the fucosyl GM1 ganglioside; (B) QS-21; and (C) a pharmaceutically acceptable carrier, wherein the fucosyl GM1 ganglioside derivative:Keyhole Limpet Hemocyanin molar ratio in the conjugate is from 400:1 to 1400:1; and the conjugate and QS-21 are each present in the composition in an amount effective to stimulate or enhance antibody production in a subject. Claims 11 and 14 provide for methods of enhancing antibody production in a subject and treating a small cell lung cancer in a subject via administration of said composition.

The claimed invention relates to applicants' *surprising discovery* that a conjugate of a derivative of fucosyl GM1 covalently bound to KLH in combination with QS-21 as an immunoadjuvant induces an immune response, i.e., an increase of IgM and IgG antibody titers, with no extreme side effects in human patients diagnosed with small cell lung cancer (SCLC).

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to

each claim. First, the cited references, when combined, teach or suggest each limitation of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Applicants maintain that none of the references cited teach or suggest each limitation of claims 1, 6-8, 11, and 14, as amended. Claims 1, 11, and 14, as amended, recite, in part, the phrase "wherein the fucosyl GM1 ganglioside derivative:Keyhole Limpet Hemocyanin molar ratio in the conjugate is from 400:1 to 1400:1." None of the cited references teach or suggest the use of any fucosyl GM1 ganglioside derivative covalently bound to Keyhole Limpet Hemocyanin in any molar ratio, and not in the claimed molar ratio range recited in amended claims 1, 11, and 14. Therefore, the references cited against amended claims 1, 6-8, 11, and 14 fail to support a *prima facie* case of obviousness since none of them discloses a key element of applicants' claimed invention.

Applicants also maintain that the cited references fail to provide a motivation to combine the teachings of the cited references, and in fact *teach away* from the claimed invention.

Jennemann et al. teaches the administration of Gfpt1 (a fucosylated GM1 ganglioside) conjugated to KLH in combination with another immunoadjuvant known as monophosphoryllipid-A ("MPL") to mice afflicted with

SCLC. Jennemann et al. recognizes that QS-21 is used as an immunoadjuvant with specific ganglioside-KLH conjugate vaccines, i.e., Glac2-KLH (see page 383, second column), GD3-KLH (see page 384, Reference no. 18), and GM2-KLH (see page 384, Reference no. 20) in studies associated with treating melanoma. However, Jennemann et al. chose instead to use MPL as the immunoadjuvant in combination with Gfpt1-KLH conjugate in treating SCLC in a subject. Jennemann et al. teaches that MPL effectively increases antibody titers within SCLC-afflicted mice, and produce antibody titers which crossreact less with Gtet1 ganglioside in mice. See Figure 1C on page 381 and page 383, second column. Thus, one of ordinary skill would conclude that Jennemann et al. teaches away from the claimed invention since it advocates use of MPL, rather than QS-21, as the immunoadjuvant of choice for fucosyl GM1-KLH conjugated vaccines.

Moreover, the Examiner stated that Jennemann et al. provides sufficient motivation for those skilled in the art to use the fucosyl GM1-KLH conjugate with QS-21 since Jennemann et al. relied on Livingston et al., Vaccine, 12(14):1275-1280. Applicants respectfully point out that Livingston et al. teaches *GM2-KLH* with QS-21 in treating *melanoma*. There is no teaching or suggestion in Livingston et al. that QS-21 would have the same effect in a composition comprising a derivative of a *different* ganglioside, such as fucosyl GM1-KLH, conjugated to KLH in treating a *different* type of cancer, i.e., SCLC, in a subject. Furthermore, the possibility that one skilled in the art *could* have arbitrarily substitute the immunoadjuvant MPL with QS-21 in a different ganglioside

conjugate does not provide the suggestion to combine references.

Vangsted et al. is directed primarily to the use of fucosyl GM1 ganglioside as a serum marker for detecting small cell lung cancer ("SCLC"). Nowhere does Vangsted et al. teach or suggest that fucosyl GM1 ganglioside be converted into a derivative with an aldehyde group which is conjugated to KLH through an amino group. Vangsted et al. further does not teach or suggest a combination of such conjugate with QS-21 as a composition used to treat SCLC in a subject.

Kensil et al. teaches the separation and characterization (with regard to adjuvant activity) of saponins, i.e., QS-7, QS-17, QS-18, and QS-21, extracted from the *Quillaja saponaria Molina* tree. Kensil et al. also teaches that crude preparations of *Quillaja* saponins have been used to boost the response to a *number* of vaccines including bovine serum albumin (BSA), KLH, sheep red blood cells (SRBC), and aluminum hydroxide-based vaccines. However, nowhere does Kensil et al. teach or suggest that any *Quillaja* saponin, e.g., QS-21, be used as an immunoadjuvant in combination with a ganglioside-KLH conjugate to treat SCLC in a subject. Kensil et al. does not use a ganglioside-KLH conjugate in combination with any *Quillaja* saponin while characterizing the *Quillaja* saponins' immunoadjuvant effects. Therefore, Kensil et al. does not provide any teaching or suggestion to one skilled in the art to use a ganglioside-KLH conjugate in combination with a particular *Quillaja* saponin, e.g., QS-21. See Kensil et al., page 431,

second column.

According to the M.P.E.P. §2143.01,

> "[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

In re Mills, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). There is simply no motivation or suggestion to combine the cited references to create the instant invention. As mentioned above, the cited references, particularly Jennemann et al., teach away from the claimed invention. One skilled in the art would be motivated to use MPL instead of QS-21 as an immunoadjuvant with a fucosyl GM1-KLH conjugate since the cited references teach successful results, i.e., eliciting an increase in antibody titers, with MPL in mice.

Applicants further maintain that the Examiner fails to provide a reasonable expectation that the claimed invention would succeed in eliciting an enhanced ability to induce an immune response based on the cited references. Jennemann et al. and Kensil et al. only disclose results based on mice. Applicants respectfully point out that the results of ganglioside-KLH conjugate vaccines in mice are not always applicable to humans. For example, a GD3-KLH conjugate in combination with QS-21 elicits a notable increase in IgG and IgM antibody titers in mice. See Table 2 of Kim, et al., "Effect of

immunological adjuvant combinations on the antibody and T-cell response to vaccination with MUC1-KLH and GD3-KLH conjugates", Vaccine, 19:530-537 (2001) (attached hereto as **EXHIBIT 3**). However, when tested on melanoma patients, the GD3-KLH conjugate in combination with QS-21 failed to elicit any increase in antibody titer response in humans. See Ragupathi, et al., "Induction Of Antibodies Against GD3 Ganglioside In Melanoma Patients By Vaccination With GD3-Lactone-KLH Conjugate Plus Immunological Adjuvant QS-21", Int. J. Cancer, 85:659-666 (2000) (attached hereto as **EXHIBIT 5**). Although Kim et al. and Ragupathi et al. were published after the priority date of the subject application, they highlight the unpredictable nature of ganglioside-KLH-based vaccines and underscore applicants' position that one skilled in the art would *not* have reasonably expected at the time of filing that the claimed invention would successfully increase antibody titer in humans.

Assuming for the sake of argument that the combination of Jennemann et al., Vangsted et al., and Kensil et al. establish a *prima facie* case of obviousness (which application vigorously dispute), applicants respectfully maintain that any such *prima facie* rejection would be rebutted by the fact that the claimed invention demonstrates an unexpected result, i.e. an increase of IgM and IgG antibody titers with no extreme side effects in human SCLC patients. As stated above, the results of ganglioside-KLH conjugate vaccines in mice are not always applicable to humans. As shown on Table 8 on page 51 (particularly the H146 data) of the instant application, despite recent intensive chemotherapy, the human SCLC

patients clearly showed an induction of an immune response. After the administration of the claimed invention, the human SCLC patients showed an increase of IgM and IgG antibody titers to *up to 10 and 3.5 times*, respectively, relative to pre-administration levels. See Table 8 on page 51 of the instant application.

As for toxicity, the claimed invention was generally well tolerated. See page 47, line 31 to page 48 to line 11 of the instant specification. Mild transient erythema and induration at the injection sites were observed in most patients, associated with flu-like symptoms. Slight increases in the severity of sensory neuropathy (by one NCI toxicity grade) were observed in six patients. However, the increases were mild, with the majority of patients reporting no change in functional capacity or progressive worsening of symptoms over time. Also, there was no evidence for diabetes mellitus, gastrointestinal or immunologic dysfunction, or other problems to suggest potential autoimmunity based on Fuc-GM1 distribution on normal tissue.

One of ordinary skill in the art would not have been able to predict, based on the cited references, whether the claimed invention would effectively induce an increase of IgM and IgG antibody titers with no extreme side effects in human SCLC patients. Therefore, applicants' claimed invention is surprising, unexpected and unobvious.

In view of the above remarks, applicants maintain that claims 1, 6-8, 11, and 14, as amended, satisfy the requirements of 35 U.S.C. §103(a).

Claim Rejection Under 35 U.S.C. §112, Second Paragraph - Indefiniteness

The Examiner rejected claims 1, 2, 5-8, 13 and 15 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner stated that claim 1 and its dependents recite the limitation "adjuvant" in line 7, and that there is insufficient antecedent basis for this limitation in the claim. The Examiner also stated that claims 6 and 7 recite the limitation "amount" in line 1, and that there is insufficient antecedent basis for this limitation in the claim. The Examiner further stated that claims 13 and 15 fail to further limit claim 12 and 14, respectively, wherein claim 13 recites the type of cancer as being small cell lung cancer, and that claims 12 and 14 already recite the cancer as being small cell lung cancer.

In response to the Examiner's rejection to claim 1 and its now pending dependents, applicants note that claim 1, as amended, does not recite the phrase "adjuvant." Instead, it only refers to "QS-21."

In response to the Examiner's rejection to claims 2 and 5, without conceding the correctness thereof, applicants have cancelled claims 2 and 5. Thus, applicants maintain that the Examiner's rejection to claims 2 and 5 is now moot, and request that the Examiner reconsider and withdraw this ground of rejection.

In response to the Examiner's rejection to claims 6 and 7, applicants note amended claim 1, in part, recites "the conjugate and QS-21 are each present in the composition in an amount effective to stimulate or enhance antibody production in a subject", and therefore, provides sufficient antecedent basis for the term "amount" recited in claims 6 and 7.

In response to the Examiner's rejection to claims 13 and 15, without conceding the correctness thereof, applicants have cancelled claims 13 and 15. Thus, applicants maintain that the Examiner's rejection to claims 13 and 15 is now moot, and request that the Examiner reconsider and withdraw this ground of rejection.

In view of the above remarks, applicants maintain that claims 1 and 6-8, as amended, satisfy the requirements of 35 U.S.C. §112, second paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejection Under 35 U.S.C. §112, First Paragraph - Written Description

The Examiner rejected claims 1, 2, 5-8, and 11-16 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner stated that the written description in this case has set forth a composition comprising a Fucosyl GM1 ganglioside (herein

fuc-GM1) conjugated to a keyhole limpet hemocyanin (herein KLH) and a QS-21 carbohydrate, and therefore, the written description in this case is not commensurate in scope to claims that read on a composition comprising a fuc-GM1 conjugated to any immunogenic protein, and further comprising any carbohydrate derived from the Quillaja saponaria Molina tree, as claimed. The Examiner stated that the written description in this case has not set forth any derivative of the fuc-GM1 ganglioside nor any derivative of KLH, as claimed.

The Examiner stated that *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing dated sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed (citing page 1117). The Examiner stated that the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (Citing *Vas-Cath* at page 1116). The Examiner stated that the applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (citing page 115).

The Examiner stated that the specification of the instant invention teaches the extraction and purification fuc-GM1 from thyroid glands of cows (citing page 20-21 of the specification) and the conjugation of fuc-GM1 to KLH (citing page 21-22). The Examiner also stated that the specification also teaches the administration of fuc-GM1-

KLH conjugate with QS-21 carbohydrate (citing page 24-28). The Examiner stated that, however, the written description in this case has not taught the broad genus of any immunogenic protein or any carbohydrate derived from the Quillaja saponaria Molina tree as claimed. The Examiner stated that, moreover, the specification has not taught "derivatives of fuc-GM1" as claimed.

The Examiner stated that there does not appear to be an adequate written description in the specification as filed of the essential structural feature that are representative of the broad genus of "immunogenic proteins," "carbohydrates" derived from the Quillaja saponaria Molina tree, or derivatives of fuc-GM1 as claimed. The Examiner stated that the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, ¶1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that the application were in possession of the genus (citing Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday, January 5, 2001, see especially page 1106, 3rd column).

The Examiner stated that the applicants do not appear to

have reduced to practice any immunogenic protein, with exception to KLH, any carbohydrate derived from the Quillaja saponaria Molina tree, with exception to QS-21, nor any derivative of fuc-GM1. The Examiner also stated that neither has the applicants provided a sufficient written description of any structure that may be correlated with the broad classes of proteins, carbohydrates or derivatives claimed. An "immunogenic protein" encompasses any molecule with the functional activity of eliciting an immune response, while a carbohydrate derived from the Quillaja saponaria Molina tree encompasses carbohydrates which have not been disclosed or isolated, and a derivative of fuc-GM1 encompasses any fragments, portion or part of the fuc-GM1 ganglioside. The Examiner stated that support for immunogenic proteins is provided in the specification on page 9, lines 25-33, where it is disclosed that an immunogenic protein refers to a protein that "stimulates or enhances antibody production in the subject." The Examiner stated that support for carbohydrates that are derived from the Quillaja saponaria Molina tree is provided in the specification on page 10, lines 10-16, where it is described as an adjuvant and encompasses "QS-21 or QS-21 like chemicals." The Examiner further stated that support for derivatives of fuc-GM1 is provided in the specification on page 9, lines 11-20, wherein a derivative is described as an oligosaccharide portion that is derived from cleaving the ganglioside or synthesized. However, the Examiner stated that no disclosure beyond the mere mention of immunogenic proteins, carbohydrates derived from the Quillaja saponaria Molina tree, or derivatives of the fuc-GM1

ganglioside made in the specification. The Examiner concluded that this is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. The Examiner further concluded that the genus of compounds encompassed by these terms is extensibe and the artisan would not be able to recognize that applicants were in possession of the invention as now claimed.

The Examiner stated that applicants were consequently not in possession of the instant claimed invention. Citing *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The Examiner stated that adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Citing *Id.* 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The Examiner stated that the disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Citing *Id.*, 43 USPQ2d at 1406. The Examiner stated that a description of what the genetic material does, rather than of what it is, does not suffice. Citing *Id.*

The Examiner stated that while it is noted that some of the instant claims are drawn to methods, the claims, nevertheless, require an adequate written description of the composition employed in the methods.

The Examiner further stated that applicants are directed to the Guidelines for the Examination of Patent Application Under the 35 U.S.C. §112, ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday, January 5, 2001, and are invited to point to clear support or specific examples of the claimed invention in the specification as filed.

In response to the Examiner's rejection to claims 2, 5, 12, 13, 15, and 16, without conceding the correctness thereof, applicants have cancelled claims 2, 5, 12, 13, 15, and 16. Thus, applicants maintain that the Examiner's rejection to claims 2, 5, 12, 13, 15, and 16 is now moot, and request that the Examiner reconsider and withdraw this ground of rejection.

In response to the Examiner's rejection to claims 1, 6-8, 11, and 14, but without conceding the correctness thereof, applicants note that claims 1, 11, and 14, have been amended. These claims, as amended, recite "a derivative of a fucosyl GM1 ganglioside which comprises a converted ceramide portion, which differs from the ceramide portion of the fucosyl GM1 ganglioside solely by having an aldehyde group in place of a double bond" and "QS-21."

In view of the amendments to the claims, applicants maintain that claims 1, 6-8, 11, and 14, satisfy the requirements of 35 U.S.C. §112, first paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner rejected claims 12, 13 and 16 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner stated that the specification, while being enabling for a method of treating small cell lung cancer comprising the administration of the composition of claim 1, does not reasonably provide enablement for a method of preventing small cell lung cancer.

The Examiner stated that the claims are drawn to a method of preventing small cell lung cancer. The Examiner stated that the specification of the instant application has only provided disclosure with regard to a method of treating small cell lung cancer, but has not specifically taught one of skill in the art how to prevent small cell lung cancer comprising the administration of a composition as claimed in claim 1.

The Examiner stated that reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. The Examiner stated that this type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The Examiner also stated that the essential element towards the validation of a

preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and link those results with subsequent histological confirmation of the presence or absence of disease. The Examiner stated that this irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. The Examiner further stated that a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease.

The Examiner stated that although the claims are drawn to the generation of an immune response to a carbohydrate, the underlying mechanism of action is based on the generation of an immune response to the administered antigen. The Examiner stated that because the mechanism is similar to peptide immunotherapeutics, the teachings of Bellone et al. and Gaiger et al. help to highlight the unpredictable nature of cancer immunotherapy and helps to underscore the importance of providing working examples for the prevention of cancer. The Examiner stated that Bellone et al. (Immunology Today, 20(10):457-462 (1999)) summarizes the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical responses" (citing page 457, 2nd column). The Examiner stated that Bellone et al. teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (citing page 461, Box 1). The

Examiner also stated that Gaiger et al. (Blood, 96(4):1480-1489 (August 2000)) chose to evaluate the Wilm's tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic cells. The Examiner stated that, however, WT1 peptide immunization did not show any effect on tumor growth in vivo (citing Figure 10, page 1486). The Examiner stated that all of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredicatable art, such as in the prevention of cancer.

The Examiner concluded that in view of the teachings above, and the lack of guidance and/or exemplification in the specification, it would not be predictable for one skilled in the art to use the pharmaceutical compositions for the prevention of small cell lung cancer as contemplated in the disclosure. Furthermore, the Examiner concluded that it would require undue experimentation by one of skill in the art to practice the invention as claimed.

In response to the Examiner's rejection, without conceding the correctness thereof, applicants have cancelled claims 12, 13, and 16. Thus, applicants maintain that the Examiner's rejection to claims 12, 13, and 16 is now moot, and request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejection Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1, 2, 5-8 and 11 as allegedly anticipated by Livingston et al. (Vaccine, 12(14):1275-1280 (1994); IDS 1/29/2002, exhibit 13). Specifically, the Examiner stated that because the metes and bounds of the term "fucosyl GM1 ganglioside derivative" have not been defined in the specification as filed, for the purposes of this rejection, a "fucosyl GM1 ganglioside derivative" is interpreted to be a GM2 ganglioside.

The Examiner stated that Livingston et al. teach a composition comprising a fucosyl GM1 ganglioside derivative conjugated to an immunogenic protein (namely KLH) a QS-21 carbohydrate, and a pharmaceutically acceptable carrier (citing page 1276). The Examiner also stated that, in particular, Livingston et al. teaches the administration of 70μg of the ganglioside (citing page 1276) and 10, 50, or 100μg of the QS-21 carbohydrate (citing page 1276). The Examiner further stated that, in addition, Livingston et al. teach that the composition is effective in eliciting an antibody response in a human (citing abstract).

In response to the Examiner's rejection of claims 2 and 5, without conceding the correctness thereof, applicants have cancelled claims 2 and 5. Thus, applicants maintain that the Examiner's rejection of claims 2 and 5 is moot, and request that the Examiner reconsider and withdraw this ground of rejection.

In response to the Examiner's rejection to claims 1, 6-8, and 11, but without conceding the correctness thereof, applicants note that claims 1, 11, and 14, have been amended. Amended claims 1, 11, and 14 recite, in part, the phrase "a derivative of a fucosyl GM1 ganglioside which comprises a converted ceramide portion, which differs from the ceramide portion of the fucosyl GM1 ganglioside solely by having an aldehyde group in place of a double bond". Applicants point out that the "derivative of fucosyl GM1 ganglioside" as recited in amended claims 1, 11, and 14, do not encompass the teachings of Livingston et al., i.e., a GM2 ganglioside. Rather, these claims solely encompass a derivative of a *fucosyl GM1 ganglioside* which comprises a converted ceramide portion, which differs from the ceramide portion of the fucosyl GM1 ganglioside solely by having an aldehyde group in place of a double bond. See instant specification, page 9, lines 11-20, and page 40, lines 26-31.

In view of the amendments to the claims, applicants maintain that claims 1, 6-8, and 11, satisfy the requirements of 35 U.S.C. §102(b), and request that the Examiner reconsider and withdraw this ground of rejection.

Supplemental Information Disclosure Statement

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following disclosures, which are listed on Form PTO-1449 (**EXHIBIT A**). Copies of the disclosures

listed below as items 1-5 are attached hereto as **EXHIBITS 1-5**, respectively.

1. PCT International Application No. WO 94/16731 A1, published August 4, 1994 (Sloan-Kettering Institute For Cancer Research) (**EXHIBIT 1**);

2. Jennemann, R., et al., "Effects of Monophosphoryllipid-A on the Immunization of Mice with Keyhole Limpet Hemocyanin- and Muramyldipeptide-ganglioside Gfptl Conjugates", J. Biochem., 119(2):378-384, (1996) (**EXHIBIT 2**);

3. Kim, S. K., et al., "Effect of immunological adjuvant combinations on the antibody and T-cell response to vaccination with MUC1-KLH and GD3-KLH conjugates", Vaccine, 19:530-537 (2001) (**EXHIBIT 3**);

4. Livingston, P. O., "Approaches to Augmenting the Immunogenicity Of Melanoma Gangliosides: From Whole Melanoma Cells to Ganglioside-KLH Conjugate Vaccines", Immunological Reviews, 145:147-166 (1995) (**EXHIBIT 4**); and

5. Ragupathi, G., et al., "Induction Of Antibodies Against GD3 Ganglioside In Melanoma Patients By Vaccination With GD3-Lactone-KLH Conjugate Plus Immunological Adjuvant QS-21", Int. J. Cancer, 85:659-666 (2000) (**EXHIBIT 5**).

A European Search Report was issued on November 11, 2004

in connection with related European Application No. 98 94 9493.5. A copy of the November 11, 2004 European Search Report is attached hereto as **EXHIBIT B**. The above-listed references 1, 2 and 4 were cited in that Search Report.

Pursuant to 37 C.F.R. §1.97(c), the required fee for filing this Supplemental Information Disclosure Statement is ONE-HUNDRED AND EIGHTY DOLLARS ($180.00), and a check which includes this amount is enclosed.

Summary

Applicants maintain that claims 1, 6-8, 11, and 14, as amended, are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $235.00 sum, which includes the $55.00 fee for a one-month extension of time and the $180.00 fee for filing a Supplementary Information Disclosure Statement, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

12/13/04

John P. White Date
Reg. No. 28,678